Attorney Docket No. 05569.0004.CNUS03

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s): McCafferty *et al.*

Application No.: 09/196,673

Filed: November 20, 1998

For: METHODS FOR PRODUCING MEMBERS OF SPECIFIC BINDING PAIRS

Group Art Unit: 1639

Examiner: Ponnaluri, Padmashri

Declaration of Dr. Ronald Henry Jackson

I, Ronald Jackson, do hereby declare and state as follows.

1. I currently hold the position of Director of Library Engineering at Cambridge Antibody Technology Ltd. I have worked in the area of protein engineering and molecular biology for over twenty years. A copy of my curriculum vitae is attached as Exhibit A.
2. I received a B.Sc. in biochemistry from the University of Edinburgh in 1977 and a Ph.D. in 1980 from the University of Birmingham.
3. From May 1990 to March 1994 I was a Senior Scientist and subsequently a Group Leader working on Research and Development on phage display of antibodies and known antibody enzymes and receptors.

4. I am an inventor of the subject matter described and claimed in the above-identified patent application (the "present application") and I have reviewed the specification and claims of that application.

5. I have also reviewed the Office Action mailed December 22, 2004 in connection with the present application. I understand that the Examiner rejected claims 46, 48-65, 78-109 and 145 under 35 U.S.C. 102(b) as being anticipated by EP 0436597 B1 ("Ladner EP" attached hereto as Exhibit B); alternatively the Examiner rejected claims 45-65, 78-109 and 145 under 35 U.S.C. 103(a) as being obvious over Ladner EP.

6. I make this Declaration specifically to address the teachings of Ladner EP and whether as of its earliest claimed priority date of September 9, 1988, Ladner EP provided an operable disclosure of methods for displaying enzymatically active enzymes at the surface of filamentous bacteriophages.

7. I have reviewed Ladner EP and I believe it does not teach displaying active enzymes at the surface of filamentous bacteriophage as claimed by the instant claims. Instead, for example, page 21, lines 29-31, Ladner EP teaches inactivating enzymes to be expressed at the surface of a filamentous bacteriophage particle such as M13. The document does not discuss an experiment where a displayed active enzyme is the desired outcome.

8. At the time Ladner EP was filed, there was a prevailing technical opinion against the success of displaying a protein on the surface of phage (e.g., antibody enzyme or receptor) that was capable of binding to a ligand. This was based on experimental data regarding the size of a protein that could be fused with the gene

3 protein published by Smith (Smith, George P (1985) Science 223: 1315-1317) and Parmley and Smith (Parmley, Stephen F and Smith, George P (1988) Gene 73: 305-318, both of which are of record in the present case. On reading the Ladner patent application in 1990 I did not feel that the disclosure would have any impact on the prevailing technical opinion because of the lack of positive experimental data and because of the language of Ladner EP itself which, at page 52, lines 7 to 9, states that each element of the proposed display methods is a potential source of failure.

9. Ladner EP gave a wide range of major modifications to try in case of lack of success in display, which would have constituted a large-scale research program with no reasonable expectation of success because Ladner EP clearly anticipated that failure was a likely outcome (*e.g.*, See Ladner EP at page 52, lines 7 to 9).

10. I have read the decision of the Technical Board of Appeals (the "Board") of 2nd July 2002 T0791/00 (attached hereto as Exhibit C) which upheld the decision of the Opposition Division of the European Patent Office (EPO) posted on 26 May 2000 revoking EP 0436597 as being completely non-operable. I have also read and analyzed documents submitted to the Opposition Division of the European Patent Office and to the Board, including all of the evidence provided to the EPO by way of the declarations of the scientific experts.

11. Based upon my own understanding of the prevailing technical opinion against the probability of successfully displaying proteins on the surface of filamentous phage in July 1990, and on the documents discussed in paragraph 10 above, I

agree with the Board that Ladner EP does not provide an operable disclosure for the display of proteins on the surface of filamentous phage.

12. I hereby declare that all statements made herein of my knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

4th August 2005
Date

Ronald Jackson
Ronald Henry Jackson

Curriculum Vitae

Name	Ronald Henry Jackson
Date of Birth	25.9.55
Place of Birth	Liverpool
Nationality	British
Education	University of Edinburgh Oct 1973 - Jun 1977 B.Sc. (Hons) Biochemistry Grade Upper second II (i) University of Birmingham Oct 1977 - Sept 1980 Ph.D. 'Purification and properties of E.coli nitrite reductase' Supervisors Dr. J.A. Cole and Dr. A.J. Cornish-Bowden

Postdoctoral Research

University of California, San Francisco Nov 1980-Sept 1982 Postdoctoral Research Scientist with Dr. Thomas P. Singer, Department of Molecular Biology, Veterans Administration Hospital

Amersham International plc (October 1982-April 1990)

Senior Scientist Development (1982-1986)

In this post I worked on the development of iodinated proteins and peptides for radioimmunoassay and receptor studies and subsequently on the development of molecular biology kits.

Project leader, Molecular BiologyDevelopment (1986-1990)

Development of molecular biology kits and systems for lambda packaging, cDNA and genomic cloning and DNA sequencing.

Cambridge Antibody Technology Ltd. (May 1990 to present)

May 1990-March1994

Senior Scientist and subsequently Group Leader working in R &D on phage display of antibodies and antibody libraries, enzymes and receptors.

March 1994-October 1997

Technical Development Manager

This role involved setting up and building a new development function at CAT and leading the project to the start of clinical trial for an antibody against TGFbeta2 for treatment of ocular fibrosis.

October 1997-May 1999 Intellectual Property Manager

Main responsibility for Intellectual Property matters both inside and outside the company. I had previously (1991-1997) been responsible for filing and examination of patent applications on a part-time basis (ca. 20%).

June 1999-May 2004 Head Product Opportunity Group

Identification of targets for CAT therapeutic programs

June 2004-date Director of Library Engineering

Development of technology for phage display and ribosome display libraries. Provision of phage display libraries to internal CAT projects and external licensees.

Bibliography

Journal Papers

1. Prosthetic groups of the NADH-dependent nitrite reductase from Escherichia coli K12.
Jackson RH, Cornish-Bowden A, Cole JA
Biochem J 1981 Mar 1 **193:3** 861-7

2. The steady-state kinetics of the NADH-dependent nitrite reductase from Escherichia coli K 12. Nitrite and hydroxylamine reduction.
Jackson RH, Cole JA, Cornish-Bowden A
Biochem J 1981 Oct 1 **199:1** 171-8

3. Relationship of the oxidation state of the iron-sulfur cluster of aconitase to activity and substrate binding.
Ramsay RR, Dreyer JL, Schloss JV, Jackson RH, Coles CJ, Beinert H, Cleland WW, Singer TP
Biochemistry 1981 Dec 22 **20:26** 7476-82

4. The steady state kinetics of the NADH-dependent nitrite reductase from Escherichia coli K12. The reduction of single-electron acceptors.
Jackson RH, Cole JA, Cornish-Bowden A
Biochem J 1982 May 1 **203:2** 505-10

5. Electron-spin-resonance studies of the NADH-dependent nitrite reductase from Escherichia coli K12.
Cammack R, Jackson RH, Cornish-Bowden A, Cole JA
Biochem J 1982 Nov 1 **207:2** 333-9

6. Inactivation of the 2-ketoglutarate and pyruvate dehydrogenase complexes of beef heart by branched chain keto acids.
Jackson RH, Singer TP
J Biol Chem 1983 Feb 10 **258:3** 1857-65

7. The biological relevance of HPLC-purified vasoactive intestinal polypeptide monoiodinated at tyrosine 10 or tyrosine 22.
Marie JC, Hui Bon Hoa D, Jackson R, Hejblum G, Rosselin G
Regul Pept 1985 Oct **12:2** 113-23

8. Distribution of vasoactive intestinal polypeptide binding sites in guinea pig genital tissues.
Inyama CO, Wharton J, Davis CJ, Jackson RH, Bloom SR, Polak JM
Neurosci Lett 1987 Oct 16 **81:1-2** 111-6

9. Anatomical distribution of vasoactive intestinal peptide binding sites in peripheral tissues investigated by in vitro autoradiography.

Power RF, Bishop AE, Wharton J, Inyama CO, JacksonRH, Bloom SR, Polak JM
Ann N Y Acad Sci 1988 **527**: 314-25

10. Phage-enzymes: expression and affinity chromatography of functional alkaline phosphatase on the surface of bacteriophage.
McCafferty J, Jackson RH, Chiswell DJ
Protein Eng 1991 Dec **4:8** 955-61

11. Selection of variants of antibodies and other protein molecules using display on the surface of bacteriophage fd
Jackson, R.H., McCafferty, J., Johnson, K.S., Pope, A.R., Roberts, A.J., Chiswell, D.J., Clackson, T.P., Griffiths, A.D., Hoogenboom, H.R. and Winter, G.
in Protein engineering: A Practical Approach ed. A.R. Rees, M.J.E. Sternberg & R. Wetzel pp277-301, IRL Press, Oxford (1992)

12. Display of functional external domains of platelet derived growth factor receptor and CD4 on the surface of bacteriophage fd
Jackson, R.H., Hoogenboom, H.R., Winter, G. & Chiswell, D.J.
Protein Engineering 1993 **6** Suppl. p114

13. Inhibition of glial scarring in the injured rat brain by a,recombinant human monoclonal antibody to.transforming growth factor-beta2.
Logan A, Green J, Hunter A, Jackson R, Berry M
Eur J Neurosci 1999 Jul **11:7** 2367-74

14. A fully human antibody neutralising biologically active human TGFbeta2 for use in therapy.
Thompson JE, Vaughan TJ, Williams AJ, Wilton J, Johnson KS, Bacon L, Green JA, Field R, Ruddock S, Martins M, Pope AR, Tempest PR, Jackson RH
J Immunol Methods 1999 Jul 30 **227:1-2** 17-29

Abstract

Jackson, R.H., Pope, A.R., Holliger, P., Prospero, T. & Winter, G. (1994) Construction and properties of bispecific diabody molecules with varying linker lengths between variable domains *J. Cellular Biochemistry* Suppl. 18D p207

Posters and Talks

New generation of monoclonal antibodies in diagnosis and therapy, Genoa, Italy April 12th-15th, 1992
Jackson, R.H., Pope, A.R., Johnson, K.S., Marks, J.D., Griffiths, A.D., Winter, G., & McCafferty,J. Isolation of specific antibodies from unimmunised humans using V-gene libraries displayed on phage

Symposium on monoclonal antibodies: Biotechnology, Havana, Cuba June 8th-12th, 1992
Jackson, R.H. Phage antibodies: will new 'coliclonal' antibodies replace monoclonal antibodies?

IBC Antibody Engineering Conference, December 1992
Johnson, K.S., McCafferty,J., Fitzgerald, K.J., Jackson, R.H., Chiswell, D.J. and Winter,G.. pCANTAB vectors: phagemid vectors for the display of antibody fragments on phage and simplified expression and purification of soluble fragments

Miami Winter Symposium: Protein Engineering and Beyond, January 17th-22nd, 1993
Jackson, R.H., Hoogenboom, H.R., Winter, G. & Chiswell, D.J. (1993) Display of functional external domains of platelet derived growth factor receptor and CD4 on the surface of bacteriophage fd

Antibody Engineering: Research and application of genes encoding immunoglobulins Keystone Symposium March 7th-13th, 1994
Jackson, R.H., Pope, A.R., Holliger, P., Prospero, T. & Winter, G. Construction and properties of bispecific diabody molecules with varying linker lengths between variable domains

Fibrosis: Keystone Symposium January 22nd-26th, 1996
Jackson RH, Williams AJ, Green JA, Vaughan TJ, Bacon L, Johnson KS, Field R, Wilton J, Ruddock S, Tempest PR and Thompson J
Human antibodies specific for human TGFbeta1 and human TGFbeta2 derived from phage display libraries

Cytokines and Disease: Keystone Symposium April 8th-14th, 2000
Jackson RH, Thompson JE and Glover DR
Fully human monoclonal antibody against human TGFbeta2 (CAT-152): from phage displayed antibody to clinical trials for reduction of scarring following glaucoma filtration surgery

Peptide Growth Factors: Gordon Research Conference August 13th-18th,2000
Jackson RH, Thompson JE and Glover DR
Fully human monoclonal antibody against human TGFbeta2 (CAT-152): from phage displayed antibody to clinical trials for reduction of scarring following glaucoma filtration surgery

Human Antibodies and Hybridomas, Dublin, October 6th-8th, 2004
Jackson RH
Antibody Drugs: In a Class of Their Own *Features and Benefits of Developing Antibodies as Drugs*

Protein Engineering Summit, Cambridge, Massachusetts, May 16th-20th, 2005
Groves M, Lane S, Jackson R, Douthwaite J, Rees G, Lowne D and Edwards B

Affinity maturation of Phage Display Antibody Populations using Ribosome Display

Patent applications

PCT/GB/01134 (WO92/01047)
Methods for producing members of specific binding pairs
McCafferty J, Pope AR, Johnson KS, Hoogenboom HR, Griffiths AD, Jackson, RH, Holliger KP, Marks JD, Clackson TP, Chiswell DJ, Winter GP, Bonnert TP

PCT/GB96/02450 (WO97/13844)
Specific binding members for human transforming growth factor beta: materials and methods
Thompson JE, Vaughan TJ, Williams AJ, Green, JA, Jackson RH, Johnson KS, Bacon L, Wilton AJ, Tempest PR, Pope AR